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Running head: Kinetic and particle energy ejection fraction

Abstract

Ventricular volumetric ejection fraction (VV EF) is often normal in patients with single ventricle circulations despite them experiencing symptoms related to circulatory failure. We sought to determine if kinetic energy (KE) could be a better marker of ventricular performance. KE was prospectively quantified using 4D flow MRI in 41 patients with a single ventricle circulation (aged 0.5 - 28 years) and compared to 43 healthy volunteers (aged 1.5 – 62 years) and 14 patients with left ventricular (LV) dysfunction (aged 28 – 79 years). Intraventricular end-diastolic blood was tracked through systole and divided into ejected and residual blood components. Two ejection fraction (EF) metrics were devised based on the KE of the ejected component over the total of both the ejected and residual components using: (1) instantaneous peak KE to assess *KE EF* or; (2) summating individual peak particle energy (PE) to assess *PE EF*. KE EF and PE EF had a smaller range than VV EF in healthy subjects (97.9 ± 0.8% vs. 97.3 ± 0.8% vs. 60.1 ± 5.2%). LV dysfunction caused a fall in KE EF (p =0.01) and PE EF (p =0.0001). VV EF in healthy LVs and single ventricle hearts was equivalent however KE EF and PE EF were lower (p <0.001) with a wider range indicating a spectrum of severity. Those reporting the greatest symptomatic impairment (NYHA II) had lower PE EF than asymptomatic subjects (p =0.0067). KE metrics are markers of healthy cardiac function. PE EF may be useful in grading dysfunction.

New and noteworthy: Kinetic energy (KE) represents the useful work of the heart in ejecting blood. This article details the utilization of KE indices to assess cardiac function in health and a variety of pathophysiological conditions. KE ejection fraction and particle energy ejection fraction (PE EF) showed a narrow range in health and a lower wider range in disease representing a spectrum of severity. PE EF was altered by functional status potentially offering the opportunity to grade dysfunction.

Keywords: [cardiac magnetic resonance] [congenital heart disease] [heart failure]

Glossary

2D	two-dimensional
4D flow MRI	four-dimensional flow magnetic resonance imaging
AVVR	atrio-ventricular valve regurgitation
bSSFP	balanced steady state free precession
CMR	cardiac magnetic resonance
CPET	cardio-pulmonary exercise testing
EDV	end diastolic volume
ESV	end systolic volume
GLM	generalised linear model
KE	kinetic energy
KE EF	kinetic energy ejection fraction
KE_{ej}	ejected kinetic energy
KE_{res}	residual kinetic energy
LV	left ventricle
NYHA	New York Heart association
PC	phase contrast
PE_{ej}	ejected particle energy
PE_{res}	residual particle energy
PE EF	particle energy ejection fraction
RPA	right pulmonary artery
RV	right ventricle
SV	stroke volume
VENC	velocity encoding
VV EF	ventricular volumetric ejection fraction

Introduction

Single ventricle physiology represents a spectrum of congenital heart disease in which one ventricle is under-developed such that the heart is unable to support both the pulmonary and systemic circulations. It occurs in approximately 4-8 per 10000 life births. (43) The condition is uniformly fatal unless patients undergo a series of staged palliative surgical procedures resulting in a Fontan circulation. (22) (41, 42) Patients with single ventricle circulations have poor long-term outcomes as they experience symptoms related to circulatory failure. (34) Accurate assessment of ventricular function is a crucial tool in picking up early signs of deterioration. At present cardiac magnetic resonance imaging (CMR) is the gold standard for assessing ventricular volume and function. (25, 37, 40) However the majority of patients with a single ventricle circulation appear to have a normal ventricular volumetric ejection fraction (VV EF) despite experiencing significant symptoms of circulatory failure (5, 14) which are likely to be due to reduced cardiac performance. (44, 54) The reasons for ejection fraction being relatively insensitive in this patient group are multi-factorial: the altered ventricular geometry and position increase the complexity of assessing function; (7) VV EF is load sensitive marker and the preload is greatly changed at each surgical stage (27) with subsequent effects on ventricular ejection; (8) and, unlike the normal left ventricle VV EF shows only modest inter-user reproducibility when applied to single ventricle hearts. (38) There is a need to develop new markers for assessing ventricular function in this group of patients.

Four-dimensional flow (4D flow) magnetic resonance imaging (MRI) measures the flow of blood within the heart and the large blood vessels draining to and from it. (20, 24, 39) The advantages of 4D flow MRI in comparison to conventional 2D flow modalities are that it is not limited to a single imaging plane, instead it provides a detailed assessment of the velocity of blood in three directions helping to capture subtle intricacies of blood flow within the moving heart. (58) 4D flow MRI can be used to extract parameters of intra-cardiac kinetic energy (KE). (4, 11, 19)

Kinetic energy forms a small but important part of the useful external work of the heart in pumping blood around the body. The remaining majority of the cardiac work is composed of internal work which is used to rearrange cytoskeletal structures; stretch elastic and viscous elements in the myosin cross bridges and maintain cell membrane potentials. Much of the internal energy consumption is released as heat energy contributing to cardiac inefficiency. (52). Recently there has been interest in measuring ventricular kinetic energy with a focus on patterns of intra-cardiac kinetic energy in health and disease to see if this could provide an additional tool in the assessment of ventricular function. (10, 21) Exploiting KE as a measure of useful cardiac work might give us a better understanding of cardiac performance.

In this study, we used 4D flow MRI to measure KE and develop and evaluate two new markers of systolic function. The first approach assessed peak instantaneous kinetic energy and was named the *kinetic energy ejection fraction* (KE EF). The second approach used a novel particle-based assessment and was named the *particle energy ejection fraction* (PE EF). We compared each technique in those with single ventricle circulations to those with established LV dysfunction and used healthy control subjects across the age spectrum to determine normal ranges. We hypothesized that metrics based on kinetic energy could act as an improved marker of function for assessing cardiac performance compared to VV EF.

Materials and Methods

Study design

Data was collected prospectively on 41 consecutive adults and children with single ventricle physiology (31 systemic right ventricle, 10 systemic left ventricle), 43 healthy volunteers (35 adults and 8 children) who acted as the negative control and 18 patients with left ventricle (LV) dysfunction (12 dilated cardiomyopathy, 4 ischaemic cardiomyopathy, 2 viral myocarditis) who acted as the positive control group.

Patients with a single ventricle circulation were recruited only at pre-Fontan and post-Fontan stages of their surgical palliation. Recruitment took place in 41 consecutive cases referred for MRI between 2012 and 2015. Patients with a systemic-pulmonary shunt (the earliest palliative stage in the first few weeks of life) were excluded from the study due to their volume loaded physiology. All healthy volunteers were without cardiovascular disease, in sinus rhythm, with normal ECG and normal blood pressure. All patients under the age of 10 years were scanned under general anaesthesia using low-dose inhaled sevofluorane with remifentanyl whilst maintaining normocarbia as per institutional preference. Selection criteria for those with LV dysfunction were any subject undergoing CMR with an ejection fraction <55% and no contra-indication to undergoing a clinical CMR scan.

Only a limited number of single ventricle subjects (n =5) had undergone cardio-pulmonary exercise testing (CPET) as most were of young age and short stature. As such an estimated assessment corresponding to the New York Heart Association (NYHA) functional classification of heart failure symptoms was performed.

All subjects underwent cardiac MRI on a 1.5T scanner (Achieva; Philips Healthcare, Best, The Netherlands). The local research ethics committee approved the study design and all participants gave written consent (09/HO802/78) (10/H0802/65).

MRI acquisition

Cine imaging

Retrospectively ECG-gated balanced steady state free precession (bSSFP) cine short axis stacks were performed with the short axis planned parallel to the atrio-ventricular valve plane of the systemic ventricle. Images were acquired during end-expiratory breath-holds covering apex to

base. Typical imaging parameters: TR 3.0-3.6ms; TE 1.5-1.8ms; Parallel imaging factor (SENSE) 2; flip angle 60°; field of view 200-400mm, slice thickness 6-10mm depending on patient size, in-plane resolution 1.3-2.0mm; acquired temporal resolution 30-40 phases (20 -30ms), breath-hold duration 5-7 seconds per slice with 10-14 slices to cover the whole heart including the proximal aorta. A 15mm respiratory gating window was used to ensure breath holds were consistent between slices. Analysis of volumetric data was performed using a Viewforum workstation (Viewforum, release 2.0, Philips Healthcare, Best, Netherlands). Segmentation of the ventricular cavity involved manual tracing of the endocardial contour for each slice at end-systole and end-diastole. (37) Additionally the cross-sectional area of the outflow tract was measured in two planes on the bSSFP images.

Two-dimensional phase contrast flow imaging

A free-breathing retrospectively ECG triggered two-dimensional (2D) phase contrast (PC) scan orthogonal to the ascending aorta at the level of the right pulmonary artery was acquired with 3 signal averages, spatial resolution of 1.5x1.5x6mm and acquired temporal resolution of 30 phases. The peak velocity (PV) of flow in the aorta was used to target the velocity encoding (VENC) range of the 4D flow PC scan. The difference between the ventricular stroke volume (from bSSFP cine imaging) and the aortic stroke volume (from 2D PC flow imaging) was used to calculate the degree of atrio-ventricular valve regurgitation (AVVR).

Four-dimensional phase contrast flow

A free-breathing prospectively ECG triggered 4D flow whole heart MRI sequence was acquired in a sagittal plane using a targeted VENC based on 2D PC aortic PV. The mean field of view was 300x70x150mm, with a spatial resolution specific to the size of the patient: small children (<20kg) 2.0mm isotropic voxels, large children and adults (20–90Kg) 2.5mm isotropic voxels, large adults (>90Kg) 3mm isotropic voxels. The number of phases was adjusted to between 24-

32 phases to acquire a temporal resolution of <35ms. Other imaging parameters included: TR 3.8ms; TE 2.4ms; Flip angle 5; acceleration ktPCA+ x 8; (35) bandwidth 500Hz. Respiratory gating for motion correction was applied giving a nominal scan time of 5-7minutes. Data was reconstructed using Matlab software to correct for Eddy currents and concomitant field gradients. (28, 29) The analysis of flow data was performed using proprietary software (GTFlow, GyroTools LLC, Zurich, Switzerland).

Calculation of Kinetic Energy

Initially the endocardial and epicardial borders of the systemic ventricle and the endocardial border of the proximal aorta were manually segmented in the first-time frame from the short axis cine stack bSSFP images using CardioViz3D software. (55) This allowed the generation of endocardial and epicardial surfaces and a separately labelled mask image comprising the ventricular myocardium, cavity and aorta. The motion of the systemic ventricle, as seen in the cine data, was tracked by an image registration based method (48–50) using the "Image Registration Toolkit" (IRTK, IXICO Limited) and used to create displacement fields. These displacement fields were used to morph the systemic ventricular myocardial mask creating a 4D ventricular mask.

Particles from the 4D flow sequence were seeded within the intra-cavity region at a density equivalent to the voxel size of the 4D flow images. Each particle was displaced using the phase contrast 4D velocity data throughout the cardiac cycle. The position of each particle for each phase of the cardiac cycle was classified by using the 4D ventricular mask. Particles that leaked outside the ventricle were discarded as this represented noise. (9) The KE of the blood particles, at time *t*, were calculated by taking the instantaneous velocity magnitude of a particle (the streamline velocity) at each time frame and applying the following formula:

$$Kinetic\ energy\ (t) = ½\ mass \times velocity^2$$

The mass of blood was derived from multiplying the mean density of blood (1060gm/mm^3) by the volume represented by each particle.

The blood particles were then divided into ejected and residual components. Ejected blood was defined as blood that started in the ventricle at end-diastole and was ejected through the aortic valve during the systolic phase. Residual blood was defined as blood that started in the ventricle at end-diastole and remained in the ventricle at end-systole. (See Figure 1)

Two energetic metrics were derived. In the first method, the peak instantaneous kinetic energy achieved by each component of blood was chosen to reflect the maximum systolic energy exerted by the heart on each blood component (See Figure 2). In the second method, a novel approach was used. An advantage of 4D flow MRI is the ability to study the motion of individual particles of blood. The individual peak energy value achieved by each particle was summated for each blood component to provide a measure of particle energy (PE). Assessing the motion of blood on a particle-by-particle basis represents a Lagrangian approach to assessing fluid dynamics. (17)

$$Particle\ energy = ½\ mass \times velocity^2$$

To compare hearts of different sizes the KE and PE values were expressed as an energy density based on the volume of the ejected and residual blood components. Ejected energy was divided by stroke volume (SV) and residual energy was divided by end-systolic volume (ESV). The resultant parameters were respectively known as iKE_{ej} or iPE_{ej}, and iKE_{res} or PE_{res}. They were

expressed in the form of *energy per millilitre* of blood (mcgJ/ml). (19)

In addition, the time and location at which each particle reached peak velocity was assessed. For the ejected blood streamline data showed this invariably occurred in the aorta. As a smaller outflow tract could cause acceleration of blood and act as a confounder in any analysis we compared the relationship between the size of the outflow tract and peak energy values.

Energy ejection fraction

The *kinetic energy ejection fraction* (KE EF) index was calculated corresponding to the following formula:

$$KE\ ejection\ fraction = \frac{KE_{ejected}}{KE_{ejected} + KE_{residual}} \text{ x } 100$$

Where:

$KE_{ejected}$ = peak total kinetic energy value of the ejected blood component during a single cardiac cycle,

$KE_{residual}$ = peak total kinetic energy of the residual blood component during a single cardiac cycle.

The *particle energy ejection fraction* (PE EF) was calculated corresponding to the following formula:

$$\text{PE } ejection\ fraction = \frac{PE_{ejected}}{PE_{ejected} + PE_{residual}} \text{ x } 100\%$$

Where:

$PE_{ejected}$ = total individual peak particle energy value of the ejected blood component during a

single cardiac cycle,

$PE_{residual}$ = total individual peak particle energy of the residual blood component during a single cardiac cycle.

These relationships determined the proportion of useful energetic work done in ejecting blood compared to the overall energetic work during systole. KE EF reflecting the instantaneous kinetic energy, PE EF representing a particle-based approach to particle energetics. These values were compared to VV EF for each patient group to determine their impact.

Statistical analysis

Statistical analysis was performed using Stata 13.1 (StataCorp, Texas). Unpaired t-tests were used for inter-group comparisons in cohorts containing only two subgroups (e.g. healthy left ventricles in adults versus children). For cohorts with three subgroups, one-way analysis of variance (ANOVA) with Bonferroni-adjusted, post hoc t-tests were used for the majority of variables, provided the assumptions for ANOVA were met (normal distribution, equality of variance). However, this did not apply for ejection fractions (VV EF, KE EF, PE EF) which were bounded by 0% and 100%, do not exhibit equal variance, and, in the case of KE EF and PE EF, were highly left skewed. Ejection fractions were thus analyzed using a generalized linear model (GLM), assuming a binomial distribution for the dependent variable and utilizing a logit link function and robust standard errors. (6) Quantile-quantile (Q-Q) plots and the Shapiro-Wilk method was used to assess for normality. Throughout a p value < 0.05 was considered significant.

Inter-user variability of the single ventricular volume segmentations and aortic flow measurements was quantified using an intra-class correlation coefficient 2-way model with absolute agreement. Measurements were sampled for 10 subjects from the systemic RV group by

two authors (JW, KP). Healthy children were age and sex matched to 8 children with single ventricle physiology and VV EF, KE EF and PE EF values were compared. The single ventricle group was also divided into age quartiles (1st quartile <6years, 2nd quartile 7-13 years, 3rd quartile 14-20 years, 4th quartile 21-28 years).

Results

Accuracy of 4D flow measurements

Four-dimensional flow was compared to 2D flow. The peak velocity measurements showed a mean bias of -0.06 m/s with the 95% limits of agreement ranging from -0.305 m/s to +0.186 m/s. There was no statistical difference in 2D and 4D peak velocity measurements between the different patient groups (healthy LV vs. single ventricle vs. LV dysfunction, $p = 0.163$) (See Figure 3). A mean of 4.8% of particles were discarded due to leakage across the myocardial border. This did not significantly differ between groups (ANOVA $p = 0.09$).

Reproducibility of ventricular volumes and aortic flow

Intra-class coefficient (95th confidence interval) was 0.97 (0.86 - 0.99) for aortic SV, 0.97 (0.80 - 0.99) for end diastolic volume (EDV), 0.95 (0.82 - 0.980) for ESV, 0.95 (0.82 - 0.98) for SV and 0.89 (0.58 - 0.97) for VV EF.

Demographics

The demographic data for each patient group is shown in Table 1. As expected from the disease etiology those from the single ventricle circulation group were younger than those from the LV dysfunction group. Eighteen subjects were recruited with LV dysfunction. There were 4 cases of ischaemic cardiomyopathy, 2 cases of viral myocarditis, 12 cases of dilated cardiomyopathy. At most there was only trivial to mild mitral regurgitation present.

Distribution of systolic kinetic energy

The percentage of particles at peak velocity during each systolic time point were plotted against the fraction of systole (see Figure 4) to permit comparison between subjects with different heart rates. Visually those with single ventricle circulations appeared negatively skewed. The Q-Q plots are shown in Figure 5. Surprisingly despite the visual skewedness, particularly in those with single ventricle circulations, when tested all groups demonstrated a normal distribution (Healthy LV $p = 0.127$; SV $p = 0.132$; LV dysfunction $p = 0.262$). In all groups, a maximum of 10% of ejected particles were at peak velocity (and therefore peak KE) at any time.

Streamline data showed maximal velocities occurred in the outflow. The effect of the size of the outflow tract on the peak systolic KE showed a weakly positive correlation ($R^2 = 0.204$, $p < 0.001$) indicating that smaller outflows were not associated with a greater velocity and, or KE (see Figure 6).

Comparison between healthy children and adults

Table 2 shows the volumetric and KE indices for healthy children and adults. Cardiac volumes display an exponential allometric change in size with patient age. However, there were no differences between healthy adults and children for VV EF ($p = 0.52$), KE indices (KE EF $p = 0.7$) or PE indices (PE EF $p = 0.3$) allowing them to be combined into one group of healthy controls. This point and the differences in age range between our study population, healthy controls and positive controls with heart failure are discussed further in the limitations section.

Comparison between the single ventricle group and control groups

Volumetric and kinetic energy data for the three different study groups is shown in Table 3, and Figure 7. For VV EF, patients with single ventricle circulation exhibited values that were very similar to healthy controls (GLM adjusted mean 60.1% vs. 60.1%, $p = 0.99$), which were both

very dissimilar to patients with LV dysfunction (GLM adjusted mean 39.6%; $p < 0.001$ for both comparisons). This was in stark contrast to the values for kinetic energy ejection fraction and particle energy ejection fraction, where single ventricle patients now yielded results similar to the diseased left ventricle group and both of which were lower than healthy controls. The single ventricle group was divided into age quartiles (Table 4). There were no differences between age groups when comparing indexed ventricular size and function (VV EF). There was some variation in the ejected and residual energy components between different age groups - but with no trend. This could reflect: (a) that a spectrum of function is detectable using parameters of kinetic energy –some single ventricles have better function than others and; (b) a larger variation was more apparent within the smaller group of older subjects.

Age and sex matching of the 8 healthy children to 8 single ventricle children (Figure 8) showed KEEF and VVEF displayed a mixed response. PEEF showed a uniform decrease in all single ventricle patients compared to their healthy counterparts and in marked difference to the varied response seen in VVEF.

The role of single ventricle morphology

The peak 2D phase contrast velocity in the aorta was recorded to assess if single LV or single RV physiology had an impact on aortic velocity. There were no differences found (Systemic LV 99 ± 32 cm/s vs. Systemic RV 112 ± 30 cm/s; p = 0.29).

Table 5 shows the morphology of those from the single ventricle circulation group including the degree of atrio-ventricular valve regurgitation (AVVR). Subjects with moderate or severe AVVR (regurgitation fraction > 25%; n = 5) had a significantly worse PE EF than those with none or only mild regurgitation (79.3 ± 12.0% vs. 92.5 ± 5.8%; p = 0.0002) with no detected differences when comparing KE EF or VV EF. There were no differences between the group with a

systemic RV and the group with a systemic LV. Both had similar sized hearts with equivalent VV EF ($p = 0.22$), PE EF ($p = 0.49$) and KE EF ($p = 0.5$).

Estimates of functional status were made in 40 of the 41 subjects (Table 5). One child was not included as they were too young (6 months old) for a reliable estimate to be made. There was no clear relationship between NHYA status and VV EF and KE EF; however, this was not the case for PE EF, which demonstrated a fall as NHYA status worsened (Figure 9). There was no significant correlation between VV EF and PE EF in the single ventricle patients ($r = 0.23$, $p = 0.15$).

The effects of ventricular preload on VV EF, KE EF and PE EF were considered by assessing the relationship to the indexed end diastolic volume (iEDV). iEDV displayed a negative correlation with VV EF ($R^2 = -0.415$, $p = 0.02$) and KE EF ($R^2 = -0.538$, $p = 0.02$), whilst iEDV did not show any association PE EF ($R^2 = -0.194$, $p = 0.3$) indicating it was less affected by volume loading conditions.

Discussion

Patients with single ventricle circulations have poor long-term outcomes (34) making accurate assessment of ventricular function a crucial tool in picking up early signs of deterioration. However, our standard way of grading ventricular function, VV EF, is often preserved despite reduced maximal oxygen consumption (VO2 max) on exercise testing. (3, 44, 54) Recently there has been interest in measuring ventricular kinetic energy with a focus on patterns of intra-cardiac kinetic energy in health and disease to see if this could provide an additional tool in the assessment of ventricular function. (10, 21) In this paper we proposed two new measures of ventricular systolic function based conceptually on kinetic energy, the KE EF and PE EF, and assessed their usefulness in patients with single ventricle circulation.

The results of this study showed that markers of function based on KE displayed a distinction in values between health and disease. The KE EF and PE EF in healthy individuals had a very small variance. In contrast, in patients with single ventricle physiology, both the KE EF and PE EF were significantly decreased, with a broader range suggesting a spectrum of impaired function. This is in marked contrast to VV EF which had a broad range in health and furthermore showed no differences in values between the two groups. The positive control group represented by subjects with LV dysfunction, where we would expect abnormalities in kinetic energy, (19, 58) showed a reduction in both KE EF and PE EF similar to the single ventricle group indicating that metrics based around systolic kinetic energy indices may offer a new tool for functional assessment across a spectrum of cardiac diseases.

Comparing differences in ventricular and kinergetic assessment

The broad range of VV EF in health makes detection of abnormalities in cardiac function more challenging with larger numbers needed to separate healthy hearts from those with reduced function. This is in part due to our method of assessing ventricular volumes. Standard CMR protocols recommend planning stacks of slices in the short axis plane parallel to the atrio-ventricular valve plane for assessment of VV EF. (36) Whilst CMR is the gold standard for volumetric assessment this process can be prone to errors that may increase the variability in measurements. (37, 40) Stacks of transverse slices offer less variability (2, 23) but not necessarily a more accurate volume. An inconsistent breath-holding position between slices leads to loss of contiguity further contributing to increased margins of error. Indeed, the large range and variability in VV EF (57) may be responsible for its poor gradation of risk in those with only mildly reduced ejection fraction. (15) The physiological adaptations undergone by those with a single ventricle circulation further contributes to the difficulty in accurate assessment of function using VV EF. Single ventricles are dilated, hypertrophic and hypocontractile. (27) They undergo

dramatic changes in loading conditions during early operative procedures that leave VV EF sensitized to preload and relatively insensitive to detecting mild cardiac dysfunction. (26) We found that as a group although patients with single ventricle physiology had an increased end diastolic volume (EDV), they also had an increased SV which led to a VV EF that was similar to the control group. The preservation of VV EF was at odds with patient reported symptomology. Whilst 16 out of 40 assessed patients with single ventricle physiology described symptoms of exercise intolerance (NYHA class II or greater) we found no relationship between VV EF and NYHA class. In contrast, KE EF and PE EF values were significantly depressed in single ventricle patients, indicating the presence of an underlying abnormality in the dynamics of energy transfer from myocardium to blood. Furthermore, PE EF fell in tandem with subjectively reported symptoms of heart failure. Those describing significant limitations in function had the lowest PE EF values. PE EF allowed stratification of function that appeared to match with reported symptomology in a way that is not permitted by VV EF or KE EF. These results are from a small sample size but warrant further work in assessing particle based measures of kinetic energy as a potential new functional biomarker.

The role of single ventricle morphology and valvular regurgitation on energetics

The reduction in KE EF and PE EF seen in those with single ventricle physiology is a multifactorial process. We assessed the impact of left and right single ventricular morphology and found no apparent differences. We additionally assessed if the severity of AVVR played a part and found a significant fall in PE EF. The severity of AVVR is correlated to the degree of volume loading on the ventricle. Those with only modestly dilated hearts frequently demonstrate compensatory changes leading to preserved function. This does not necessarily reflect the work performed by the heart in ejecting the recirculating regurgitant blood volume. Altered energy efficiency has been demonstrated in computational models (16) and the changes in PE EF may reflect this altered energy efficiency.

Relevance to previous studies

Previous studies performed using 4D flow MRI have assessed the intracardiac KE in healthy hearts (11, 20, 24), established values through a range of ages (58) and also investigated the impact of heart failure on normal kinergetics. (19, 32, 53) In one study KE was used to assess function in Tetralogy of Fallot, a form of congenital heart disease, with mixed results. Importantly these studies have all assessed the peak kinetic energy of the total blood volume. This study used a previously validated method to derive KE (58) Two different measures of energetic ejection fraction were then assessed. The KE EF used a similar principle of measuring peak total KE as compared to the existing body of published work. However, a second method based on a particle-by-particle analysis was also evaluated. The use of PE EF represented a novel approach to assessing kinetic energy in the heart. It utilised the advantages of particle analysis afforded by 4D flow MRI, with advances in computational processing to permit detailed kinematic analysis of blood flow. The importance of a Lagrangian approach to assessing particle energetics and fluid dynamics becomes clear when considering that at any instance a maximum of 10% of particles are ever at peak velocity. Assessing whole blood volumes in this way may underestimate the total work of the heart. The area of energetics is an emerging topic and further work is currently being performed to compare energetics in healthy hearts to those with heart failure (32, 45, 53, 60) and there is much potential to expand this into congenital heart disease to help us better understand these conditions.

Limitations

The majority of the patients with single ventricle physiology in our study were children, but it was difficult to match a healthy volunteer cohort with similar age range with only eight of our healthy volunteers being children. However, when analysed as separate groups, the energetic parameters in our adult and children healthy volunteers were remarkably similar, with a narrow

range in both children and adults. For our positive controls, we were unable to include any children in the heart failure group as none underwent cardiac MRI during the study period. However as there were no differences between the adults and children in the healthy control group then we would expect our positive controls to be a reasonable comparative group. This study represents an initial study into the uses of kinetic energy in relation to function. We have demonstrated that as a biomarker there are promising early results. Further work in this area should include expanding the population studied in both health and different diseases to understand the physiological impact.

4D flow MRI was acquired using a free-breathing technique only during expiration, which loses the normal respiratory variation in flow. There was no significant difference between the peak velocities of different groups measured by signal averaged free breathing 2D or 4D flow indicating no systematic bias caused by patient size or morphology. The highly accelerated 4D flow sequence allowed us to acquire at an isotropic spatial resolution of 2.0-3.0mm and a true temporal resolution of <35milliseconds falling within previously defined recommendations for accurate flow acquisitions. This resolution was comparable to other published 4D flow literature.

The patients in this study were anaesthetised using sevofluorane and remifentanil. Patients were managed with the lowest doses required to maintain effective anaesthesia. The effects of sevofluorane on loading conditions and contractility has been widely studied in animals. (1) A dose dependent effect is seen with decreased systolic arterial pressure, heart rate, cardiac index, left ventricular minute work, maximum rate of rise of left ventricular pressure, and systemic vascular resistance. There were no demonstrable effects on stroke volume and left ventricular end-diastolic pressure. High-dose remifentanil has been shown to reduce stroke volume, heart rate, and mean arterial blood pressure. (33) These anaesthetic agents appear to act in synergy altering cardiac loading conditions and contractility differently to their individual actions.

Chanavaz et al (13) assessed a group of children undergoing anaesthesia using echocardiography to record ventricular function initially with sevofluorane and then following the addition of remifentanil. The addition of remifentanil reduced heart rate, blood pressure and cardiac index. However, it caused an increase systemic vascular resistance with a fall in contractility which is not in keeping with the actions of either drug alone. Importantly the effects of these anaesthetic drugs are dose dependent. Through maintenance of effective anaesthesia with the lowest possible dose required we have attempted to minimise these haemodynamic effects. Earlier studies carried out by our group (46) have compared cardiac function in a control group of awake healthy adult subjects to children with Single ventricle physiology anaesthetised with a similar protocol to this study. We recorded similar baseline values of preload (47) and ventriculoarterial coupling (51). This indicates that through using low dose anaesthetic agents and careful management of physiological parameters it is possible to alleviate the haemodynamic effects of higher dose general anaesthesia.

Although MRI 4D flow is now becoming increasingly available on scanners with the latest generation software, the technical expertise to perform detailed post-processing to calculate kinetic energy is less generally available. As familiarity grows with this concept we hope that our work to improve post-acquisition and processing analysis (12) may prove invaluable for increasing accuracy and reliability of such sequences and lead to increased clinical integration. In addition, in the future it may be possible to acquire the 4D flow data using novel echocardiographic techniques that would make data acquisition much simpler and possible at the bedside or in the clinic. (30) In the future dual VENC sequences will lead to improved accuracy of flow and KE measurements through improved signal-to-noise ratio. (18)

Future work correlating functional measures via CPET to measures of kinetic and particle energy parameters would be useful to determine if these reflect objective measures of exercise tolerance.

In this instance, the size of the patients was a limiting factor but as more patients with this physiology grow into adulthood this should become increasingly possible. Early work is being carried out using supine exercise within the CMR environment. (56) As this technology becomes more refined then exercise CMR could be performed which could unmask evidence of dysfunction which may not always be seen during resting states. (59)

The density of blood taken was assumed to be 1060gm/mm^3 for all cases. This can alter in those with cyanotic heart disease. The haematocrit for the single ventricle group was measured prior to anaesthesia and was within the normal range for all but three patients. The literature suggests a large change in haematocrit from 0.30 to 0.60 is required to cause a small 1.9% increase in the blood density from 1040gm/mm^3 to 1060gm/mm^3 permitting the use of a mean blood density value. (31)

Conclusions

Kinetic energy parameters offer new insight into the function of the heart. They are consistent in health and show deviation in cardiac disease particularly in conditions such as single ventricle physiology where standard ejection fraction values are often normal. Further work to determine its relationship with other prognostic outcomes would allow full implementation as a clinical tool.

Acknowledgements

The Image Registration Toolkit (IRTK) was used under License from Ixico Ltd.

Grants

The Division of Imaging Sciences receives support as the Centre of Excellence in Medical Engineering (funded by the Wellcome Trust and EPSRC; grant number WT 088641/Z/09/Z) as well as the BHF Centre of Excellence (British Heart Foundation award RE/08/03).
The authors acknowledge financial support from the Department of Health via the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's & St Thomas' NHS Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust.

Disclosures

None

Conflict of Interest

None

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Figures

Figure 1: Ejected and residual blood components derived from 4D flow MRI. Red particles represent the residual blood component and green particles show the ejected blood component

Figure 2: Typical kinetic energy curves for the ejected and residual blood components in a healthy volunteer. To allow for different heart rates the time is indexed as a fraction of total length of systole. The instantaneous peak kinetic energy value is recorded.

Figure 3: Bland Altman plots of 2D PC and 4D PC flow stroke volume and peak velocity measurements

Figure 4: Percentage of particles at peak velocity at each point through systole. All groups demonstrate a normal distribution.

Figure 5: Quantile-Quantile plots of expected vs. observed values for percentage of particles at peak velocity during systole.

Figure 6: Peak ejected kinetic energy against outflow tract size. Smaller outflows are not associated with increased velocity or KE.

Figure 7: Box and whisker plots showing relationship between patient group and ejection fraction for all patients. KEEF and VVEF are shown in the top panel. PEEF and VVEF in the bottom panel. P values are shown for inter-group comparisons, and are calculated post hoc from the Generalized Linear Model using the Bonferroni adjustment.

Figure 8: Changes in KE EF (above) and PE EF (below) against VV EF for 8 healthy children compared to 8 age and sex matched single ventricle patients. The origin point is used as the index for all healthy controls. The arrows demonstrate how the ejection fraction differs for each age-sex matched case. Values to the left of the origin represent a decrease in VV EF whilst values below the origin indicate a decrease in KE EF or PE EF.

Figure 9: Box and whisker plots showing relationship between NYHA status and ejection fraction for single ventricle patients. KE EF in the left panel, PE EF in the middle panel, VV EF in the right panel. P values are shown for inter-group comparisons, and are calculated post hoc from the Generalized Linear Model using the Bonferroni adjustment.

Tables

Table 1: Kinetic energy function study: patient demographics.

F = female, M = male, BSA = body surface area, HR = heart rate, BP = blood pressure, LV = left ventricle

Table 2: MRI derived volume indices for healthy adults and children.

iEDV = indexed end diastolic volume, iESV = indexed end systolic volume, iSV = indexed stroke volume, VV EF = ventricular volumetric ejection fraction, iKE_{ej} = kinetic energy density for ejected blood, iKE_{res} = kinetic energy density for residual blood, KE EF = kinetic energy ejection fraction, iPE_{ej} = particle energy density for ejected blood, iPE_{res} = particle energy density for residual blood, PE EF = particle energy ejection fraction, LV = left ventricle

Table 3: MRI derived volumetric and kinetic energy indices for healthy control, single ventricle and left ventricle dysfunction groups.

iEDV = indexed end diastolic volume, iESV = indexed end systolic volume, iSV = indexed stroke volume, VV EF = ventricular volumetric ejection fraction, GLM = generalised linear model, iKE_{ej} = kinetic energy density for ejected blood, iKE_{res} = kinetic energy density for residual blood, KE EF = kinetic energy ejection fraction, iPE_{ej} = particle energy density for ejected blood, iPE_{res} = particle energy density for residual blood, PE EF = particle energy ejection fraction, LV = left ventricle

Table 4: MRI derived volumetrics and energetics for single ventricle subjects divided into age quartiles.

iEDV = indexed end diastolic volume, iESV = indexed end systolic volume, iSV = indexed stroke volume, VV EF = ventricular volumetric ejection fraction, iKE_{ej} = kinetic energy density for ejected blood, iKE_{res} = kinetic energy density for residual blood, KE EF = kinetic energy ejection fraction, , iPE_{ej} = particle energy density for ejected blood, iPE_{res} = particle energy density for residual blood, PE EF = particle energy ejection fraction, LV = left ventricle

Table 5: Single ventricle morphology and functional status.

HF = Hemifontan, F = Fontan, ccTGA = congenitally corrected transposition of the great arteries, DORV = double outlet right ventricle, IVS = intact ventricular septum, DILV = double inlet left ventricle, APC = aorto-pulmonary collateral vessels, VSD = ventricular septal defect, NYHA = New York Heart Association functional class